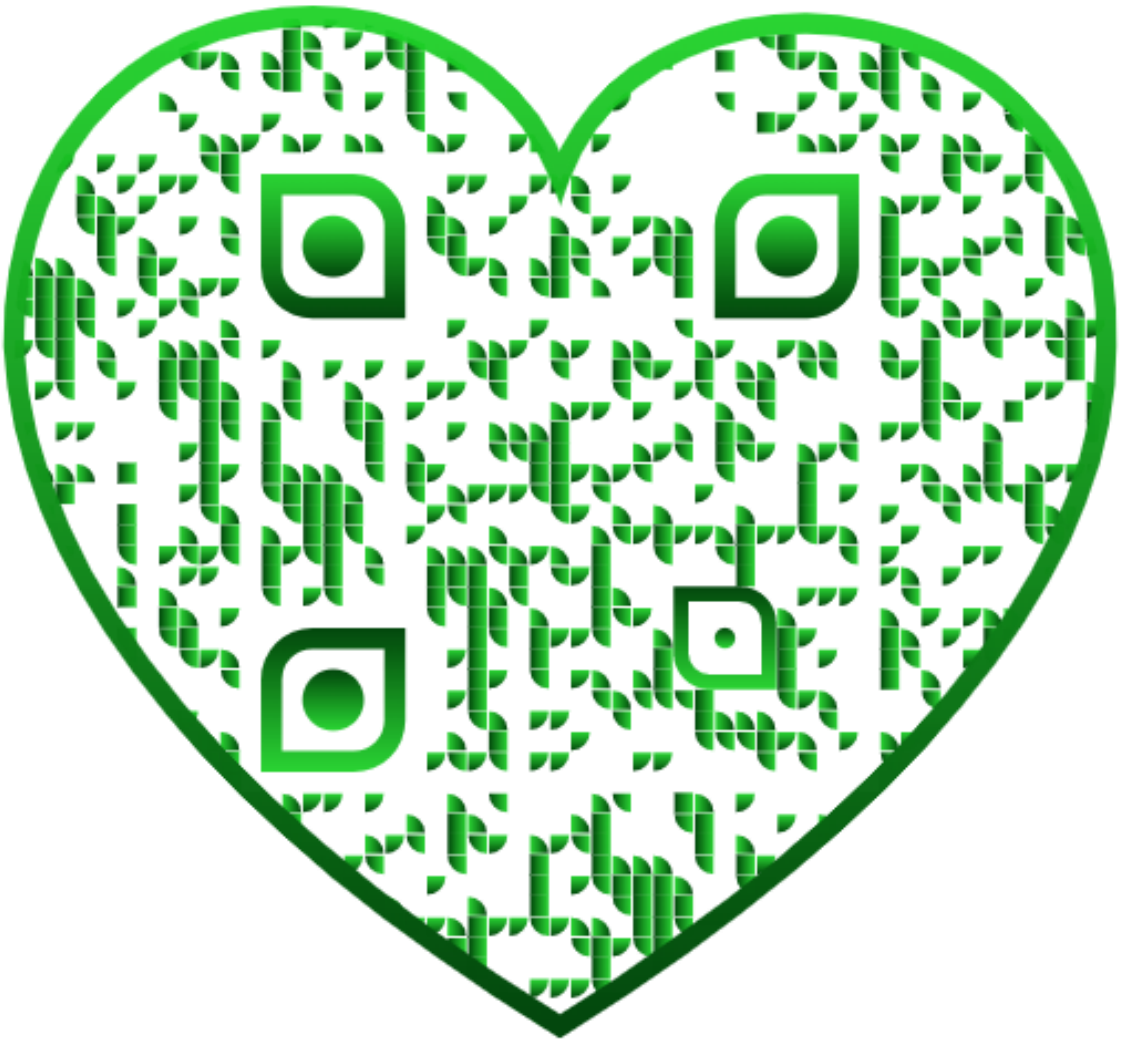
2020

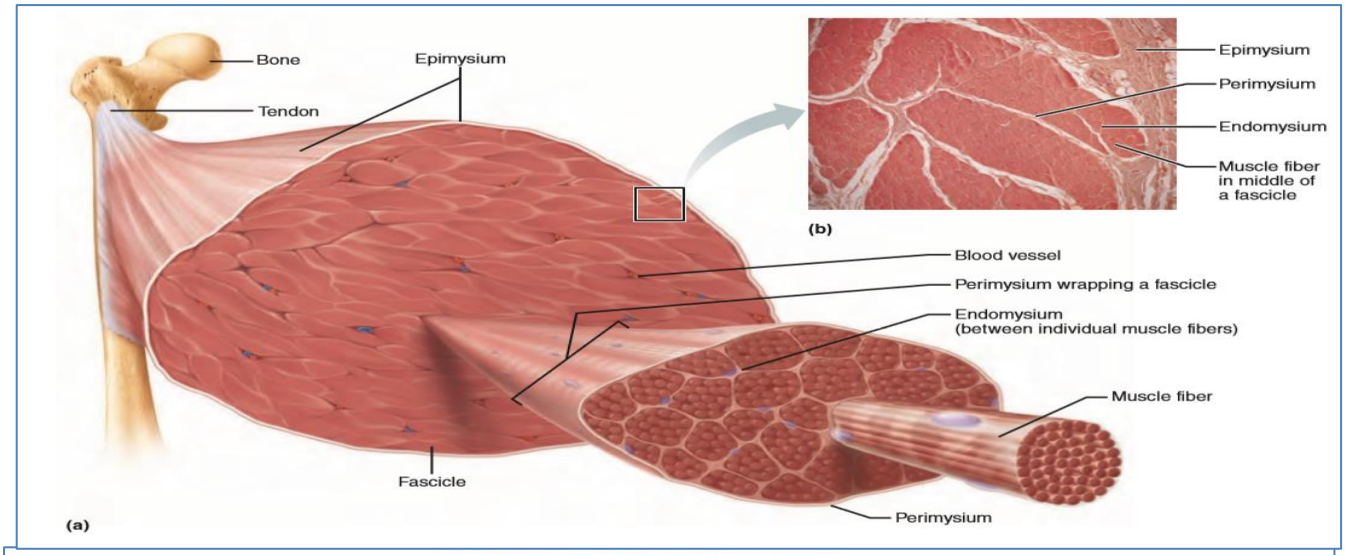
PHYSIOLOGY
FIRST YEAR

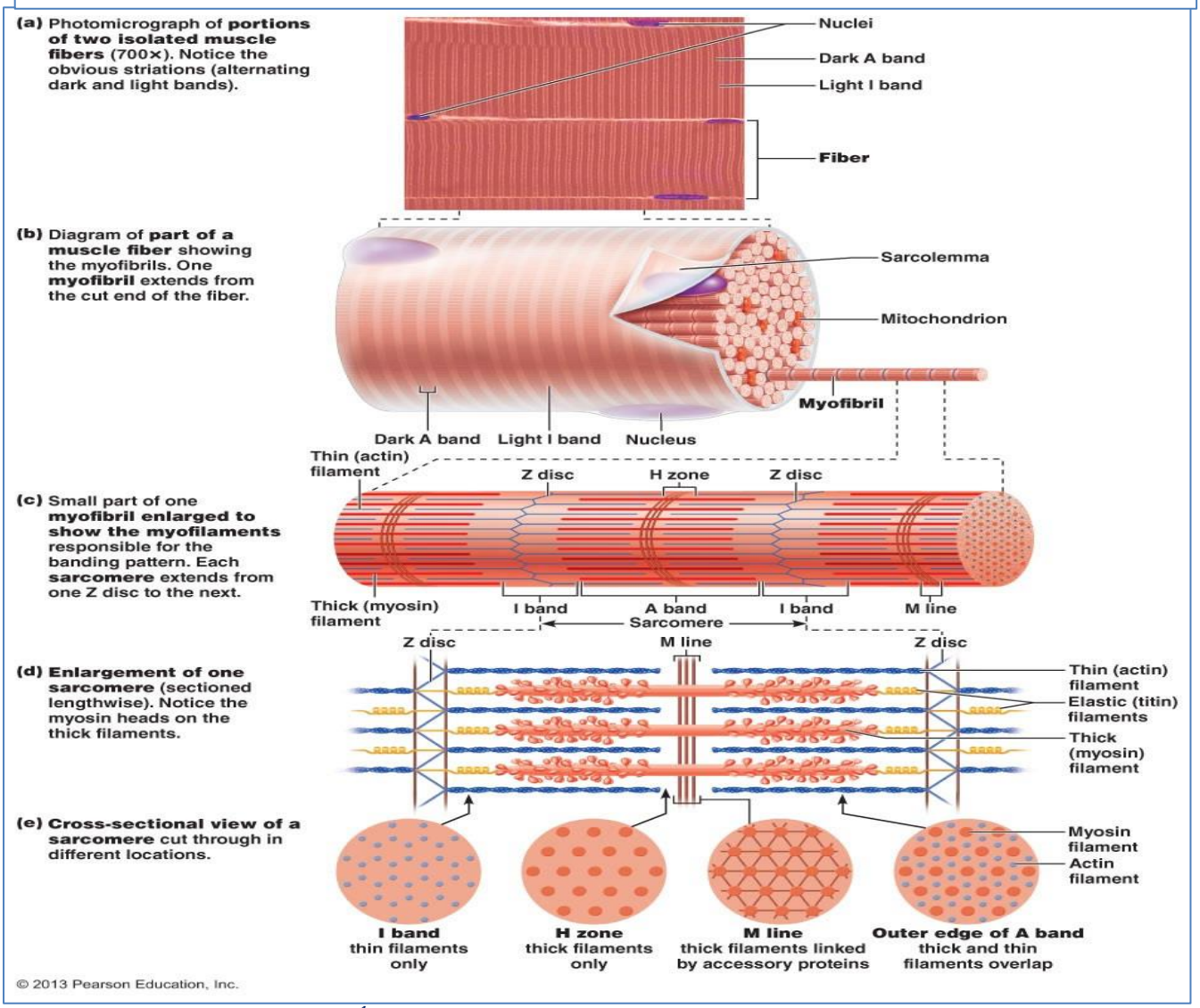
Muscle

Dr/ NAGEEB



Skeletal muscle





ثق في نفسك .. انت عبقري ، ومن دواعي شرفي هي معرفتك .. فأنت فخري وسط الناس
د/نجيب ☺

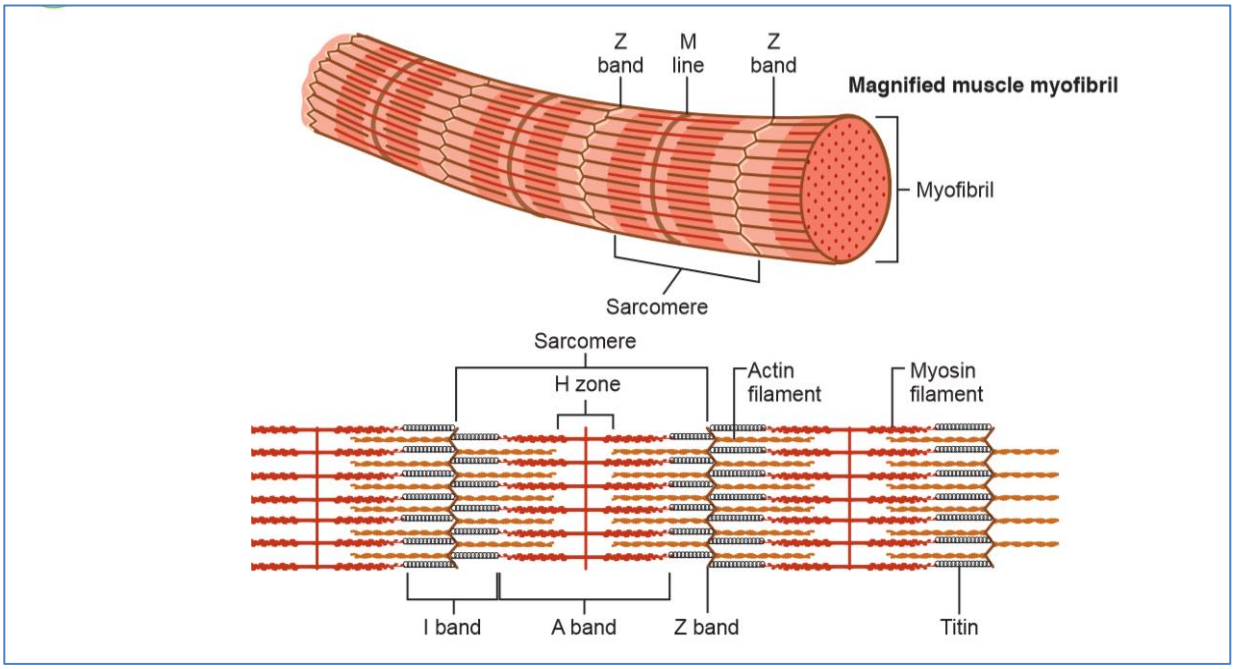
🕮 Histology of the skeletal muscle:

- The muscle is formed of large bundles called **F**ascicles.
- Each fascicle is formed of **F**ibers which is → a single cylindrical elongated multinucleated cell.
- Each fiber contains several hundreds myo**F**ibrils.
- Each myofibril consisted of several **F**ilaments → arranged in special pattern called the ***sarcomere***
- These filaments are made up of the
  - **contractile** proteins (actin & myosin)
  - **regulatory** proteins (troponin & tropomyosin) and other proteins.
- **Sarcomere** is the **contractile functional unit of skeletal muscle**.

Muscle → Fascicles → Fibers → myofibris → sarcomere → proteins and filaments

🕮 SARCOMERE is formed of:

Dark band	Light band
Called **A** band (**A**nisotropic to light).	Called **I** band (**I**sotropic to light).
100 A° in diameter.	50 A° in diameter.
Contains thick **myosin** filaments + ends of actin filaments.	Contain thin **actin** filaments + troponin + tropomyosin.
Has lighter central H-zone (has no actin filaments). Has M-line in middle of H-zone	Contain central Z-line (site of attachment of thin filaments). Sarcomere is the area between two Z-lines.



🕮 Sarcotubular system:

- It is a system of tubules present in sarcoplasm of muscle fiber. It is made of:

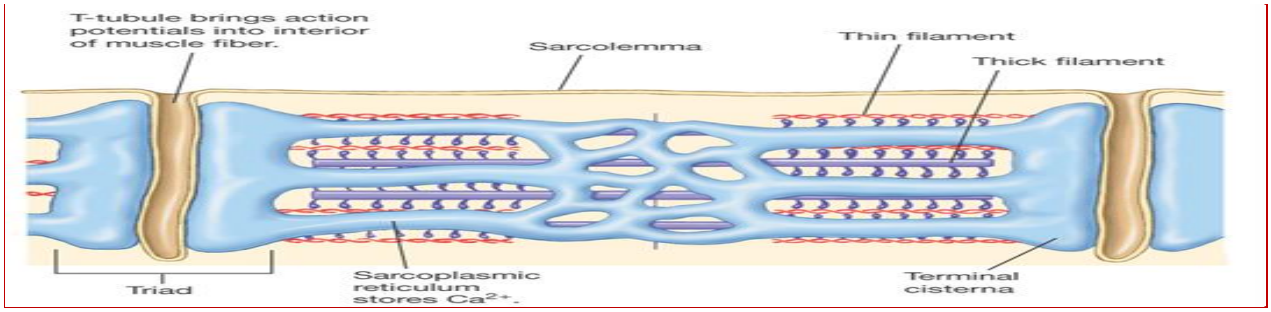
1) T- tubules (transverse system):

- It is a deep , enfolding , perpendicular on myofibril filled with **ECF**.
- **Function**: Transmission of **action potential** from cell membrane to myofibrils.

2) The sarcoplasmic reticulum:

- It is formed of longitudinal tubules parallel to the muscle fiber.
- At site of contact to T-tubules, it is dilated to form terminal Cisterns.
- **Function**: Source of Ca^{++} ions.

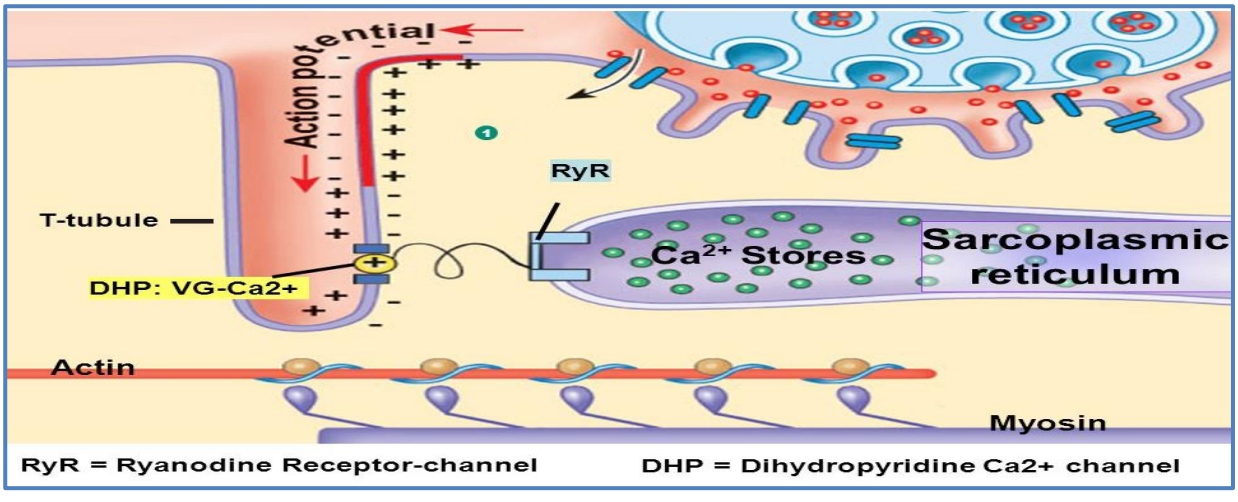
- Each 2 terminal cisterns with adjacent T-tubule is called **TRIAD**.



🕮 Mechanism of work of sarcotubular system:

- Stimulation of the sarcolemma by **end-plate-potential** → Summated to **Action potential** ⇨ Transmission of **AP** via T-tubule ⇨ Stimulate di-hydro-pyridine (**DHP**) receptor ⇨ Open **Ryandine** channels in the cisterns ⇨ Release of Ca^{++} required for muscle contraction.

- **DHP** is a voltage-gated Ca2+ channel → functions as a voltage-sensor.
- When skeletal muscle is at rest, **DHP** blocks **Ryandine**



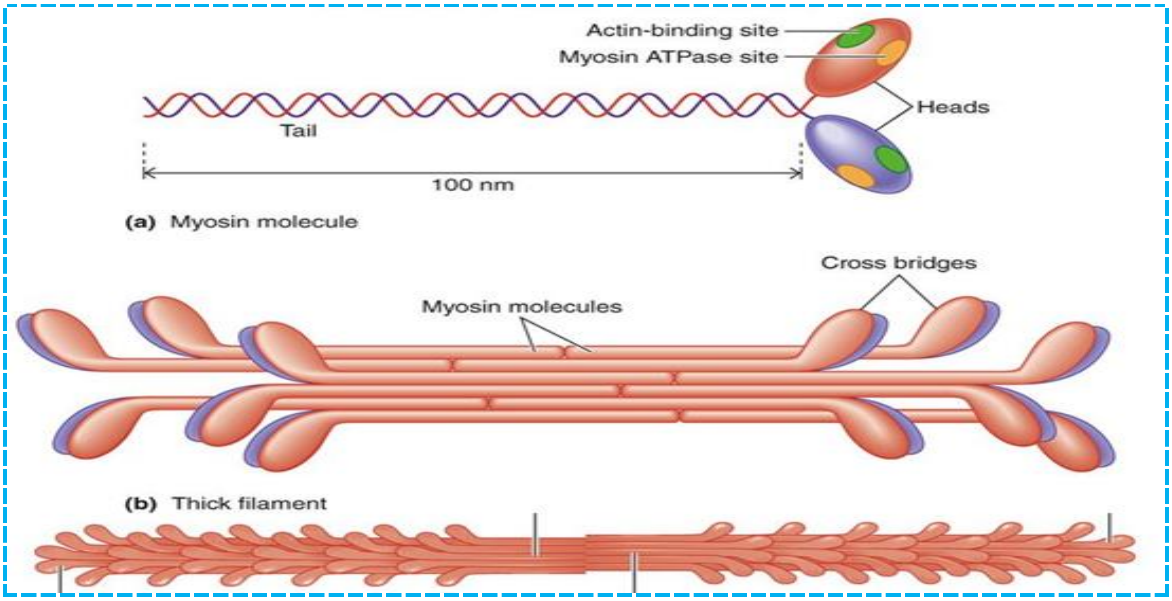
كُنّا دائِمًا محطات للغير ... ولَمْ نَكُنْ ولا مرة وجهة الطريق أو الموعد

Muscle proteins

[A] Contractile proteins:

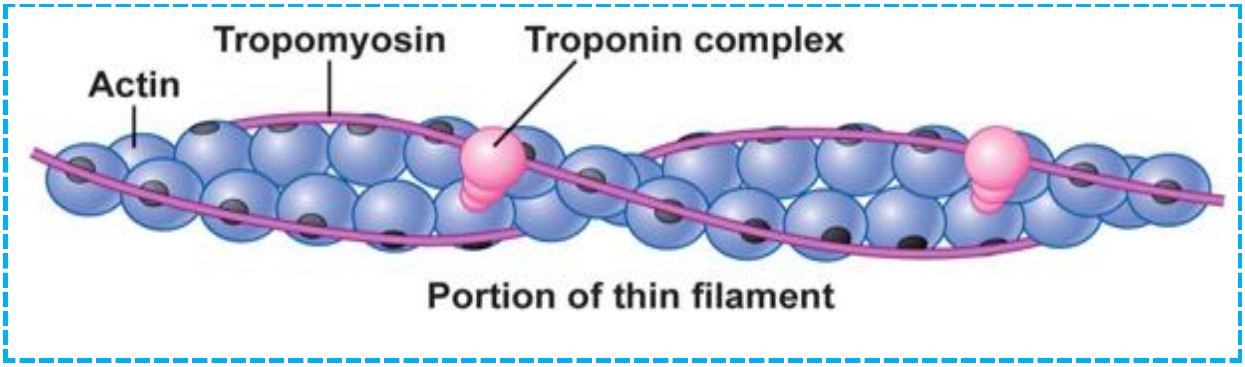
1) Myosin:

- Myosin is a complex protein
- Composed of 6 polypeptide chains (2 heavy & 4 light).
- The 2 heavy chains folded around each other as double helix forming long tail and arms.
- While the terminal part of heavy chains combine with the 4 light chains forming 2 globular heads.
- Head contains 2 sites: **A**ctin-binding site & **A**TP hydrolysis site.
- Cross bridges arise from the head at 2 flexible points called **hinges** to bind to the actin (one between the arm & tail and the other between the arm & heads).



2) Actin:

- It is a small globular protein (MW = 42,000).
- The globules are attached to each other to form filaments arranged in two chains as long double helix.



[B] Regulatory protein:

1) Tropomyosin: (inhibitory protein)

- It is a long filament located between the 2 chains of actin.
- It **covers the active sites** of actin which combine to myosin .. **So ?**
  - ➔ It **inhibits** binding of actin to myosin … **but baby ! only during rest.**

2) Troponin:

- Small globules located at intervals along tropomyosin
- Formed of 3 subunits:
  1. **Troponin T:** it binds troponin to **T**ropomyosin.
  2. **Troponin I:** it **I**nhibits binding of actin to myosin.
  3. **Troponin C:** it binds **C**a^{++} ions ⇨ **C**ontraction.

[C] Other proteins:

1) **Myoglobin:** O_2 storage protein.

2) **Elastic proteins:** a) Serial elastic component - SEC (tendon).
   b) Parallel elastic component - PEC.

3) **Supporting proteins:**

a) Actinin: binds actin to the Z lines.

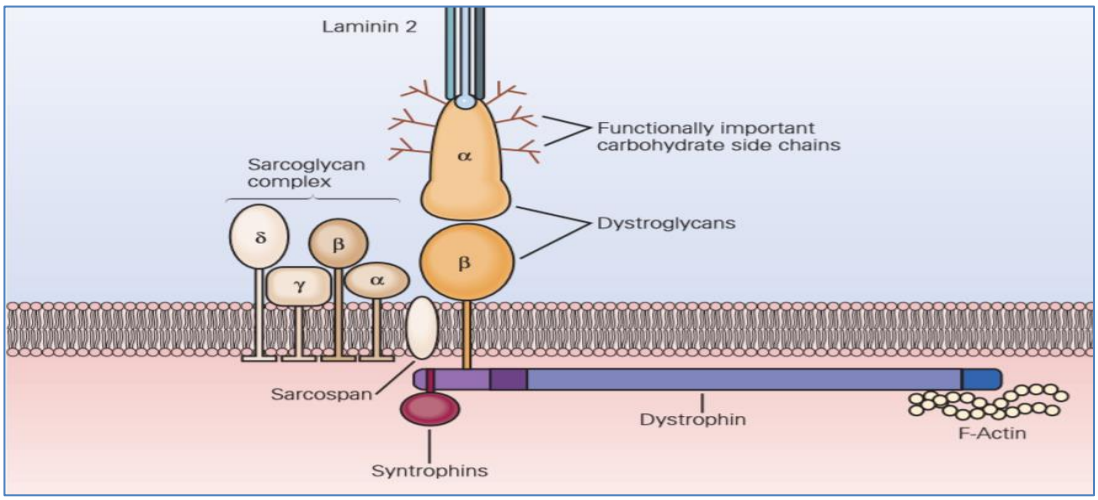
b) Nebulin: Support Actin filaments

c) Titin: connects the Z line to the M line.

d) tropomodulin

e) Dystrophin-glycoprotein complex:

- **Dystrophin** is a protein that forms a rode to connect the actin filaments to the trans-membrane protein **β-dystroglycan** in the sarcolemma by **syntrophin**
- Then, **β-dystroglycan** is connected to **laminin** in the extracellular matrix by **α-dystroglycan**.
- The dystroglycans are in turn associated with a complex of four transmembrane glycoproteins: **α-, β-, γ-, and δ-sarcoglycan**.
- This complex provides structural support to the muscle.
- So, its congenital defect causes muscle dystrophy (myopathy).



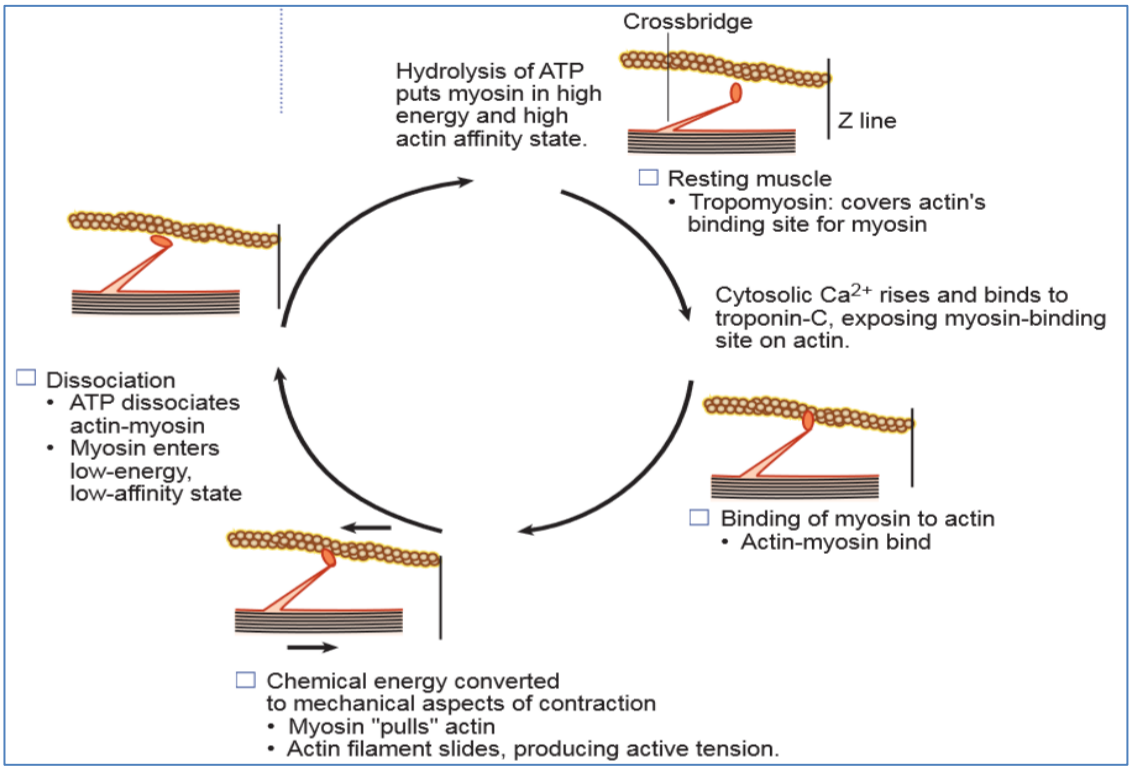
Mechanism of muscle contraction

🕮 Excitation - contraction coupling:

- It is the process by which **depolarization** of the muscle fiber initiates **contraction** of muscle.
- It passes with the following steps:

1 – 8 (as in neuromascular junction → See later).

1. Action potentials in the sarcolemmal membrane are propagated to the T tubules **why ?** → the T tubules are continuous with the sarcolemmal membrane
2. Depolarization of the T tubules causes change in their ***dihydropyridine receptors***. This conformational change opens Ca2+-release channels (***ryanodine***) on the sarcoplasmic reticulum
3. The concentration of **C**a^{++} increases and initiates contraction by binding to troponin-**C** leading to:
   a) **Weakness** of the binding of **troponin I** to actin.
   b) **Movement** of **tropomyosin** laterally into the groove between the thin filaments ⇨ **uncovering** binding sites of actin for the myosin heads.
4. The interaction between actin & myosin heads leads to **sliding** of actin filaments between myosin filaments ⇨ muscle contraction.
5. The energy is provided by breakdown of **ATP** by ATPase activity of myosin heads in the presence of Ca^{++} ions.

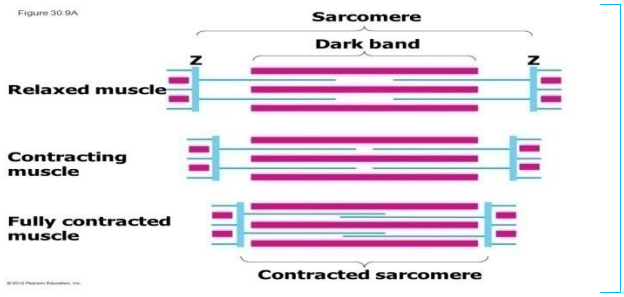

Crossbridge
Hydrolysis of ATP puts myosin in high energy and high actin affinity state.
Z line
Resting muscle
• Tropomyosin: covers actin's binding site for myosin
Cytosolic Ca2+ rises and binds to troponin-C, exposing myosin-binding site on actin.
Binding of myosin to actin
• Actin-myosin bind
Chemical energy converted to mechanical aspects of contraction
• Myosin "pulls" actin
• Actin filament slides, producing active tension.
Dissociation
• ATP dissociates actin-myosin
• Myosin enters low-energy, low-affinity state

Molecular basis of contraction:

- It is called (**ratchet** or **walk along** or **sliding theory**).
- Once the **A**ctin filaments becomes **A**ctivated by Ca^{++}, the heads of the cross bridges of myosin **A**ttach to the active sites of actin.
- The head **tilts** towards the arm and **drag** the actin filament towards the **center** of the sarcomere (towards the H zone).
- This tilt is called **power stroke**.
- **A**fter tilting of myosin head, **A**TP binds to myosin head leading to **detachment** of myosin head from actin sites and moves back to its normal direction to become in contact with **new active site** and repeat the cycle.
  Part of ATP energy ⇨ return of myosin head to its normal **P**osition.
  The other part ⇨ stored in myosin head for next **P**ower Stroke.
- The more the **C**ross bridges the stronger the **C**ontraction.

Results of contraction:

1) The sarcomere becomes shorter.
2) The width of I band is decreased.
3) H-zone becomes narrow and may disappear.
4) The width of **A** band is remained **constant**.



Mechanism of muscle relaxation:

- By **active** reuptake of Ca^{++} to sarcoplasmic reticulum by active Ca^{++} pump.
- Breakdown of **ATP** is necessary to Ca^{++} pump.
- Decrease the intracellular Ca^{++} ions to **10^{-7} mol/L**, the troponin-tropomyosin complex return to its **original position** separating myosin head from actin that is covered and inhibited by tropomyosin resulting in muscle relaxation.
- So, ATP needed for contraction & relaxation.

Cross-bridge cycling (contraction) continues until

1- **Withdrawal of Ca2+:** cycling stops at (normal resting muscle)
2- **ATP is depleted**: cycling stops at contraction state → **contracture or rigor**
this would not occur under physiologic conditions

وتظن أنك بحاجه شديدة للإختفاء بينما أنت في أمس الحاجة لمن يجدك فقط

Changes that accompany muscle contraction

- The muscle contraction is associated by:
  (Electrical & Excitability & Metabolic & Thermal & Mechanical) changes.

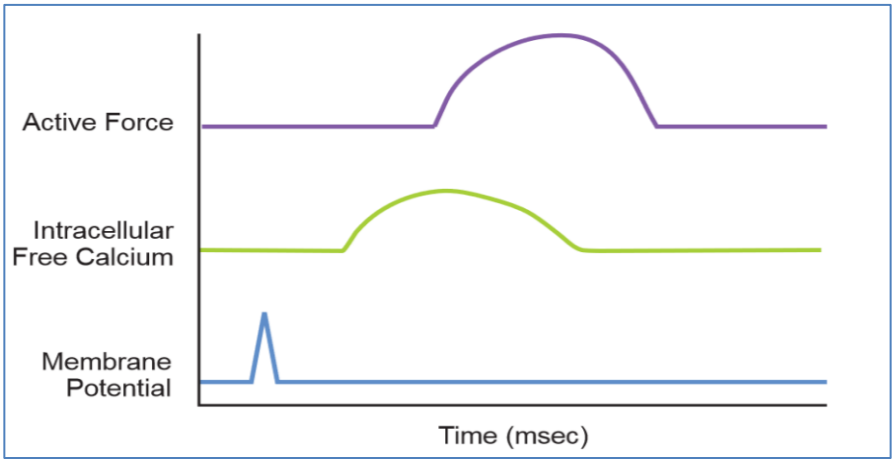
[I] ELECTRICAL AND IONIC CHANGES

- Similar to the nerve with the following differences:

	Muscle	Large nerve	Medium nerve
RMP	**- 90 mV.**	**-90**	**-70**
Firing Level (Threshold)	**- 70 mV.**	**-65**	**-55**
Overshoot	**+ 40 mV.**	**+35**	**+30 or +35**
Amplitude of AP	**130 mV.**	**125**	**100 or 105**
Duration of spike P.	2-4 msec.	2 msec.	
Rate of conduction	5 meter/sec.	Variable.	
Chronaxie	Long (less excitable).	Short (more excitable).	

[II] EXCITABILITY CHANGES

- Similar to nerve. **but .. baby !!!!!!!** →
- **Contraction** phase in the skeletal muscle starts **after** the end of the **ARP**. هاااام



[III] METABOLIC (CHEMICAL) CHANGES

🕮 Energy needed for muscle:

1. **At rest:** for RMP & formation of glycogen & muscle tone.
2. **During contraction:** for cross bridges and shortening.
3. **During relaxation:** for Ca^{++} pump.

- During contraction: Metabolic rate is markedly increased.

🕮 Source of energy:

- ATP hydrolysis ⇨ ADP + H_3 PO4 + 7.3 Kcal.
- Then there is reformation of ATP.

🕮 Reformation of ATP by:

1) ADP + **creatine phosphate** $\xrightarrow[\text{phosphokinase}]{\text{creatine}}$ ATP + creatine. (limited source).

2) ADP + **ADP** $\xrightarrow{\text{Myokinase}}$ ATP + AMP. (limited source).

3) **Glycogen** ⇨ Glucose ⇨ pyruvic acid.

   a) **If O_2 supply is adequate (aerobic glycolysis):**

   - Pyruvic acid $\xrightarrow[\text{cycle}]{\text{Kreb}}$ $CO_2 + H_2O$ + 38 ATP
   - This is (slow & unlimited source).

   b) **If O_2 supply is inadequate (anaerobic glycolysis):**

   - Pyruvic acid $\xrightarrow[\text{glycolysis}]{\text{anaerobic}}$ lactic acid + 2ATP
   - This is (fast & limited source).
   - It is limited source, as lactic acid accumulation ⇨ ⇩ pH of the muscle ⇨ inhibition of enzymes.

4) **fatty acids** oxidation ⇨ $CO_2 + H_2O$ + energy.

   - This source of energy is the major and unlimited source.
   - So, this is the base of physical training in the treatment of obesity.

🕮 Fates of lactic acid:

1. Diffuse to blood, then to the **L**iver to be converted to **glycogen** through **Cori cycle**.
2. **I**ncrease **heart** rate and **respiratory** rate.
3. Vaso**D**ilator to **blood vessels** of active muscle.
4. Oxidized to pyruvic **A**cid during the **recovery** period.
   Then, pyruvic acid ⇨ 38 **A**TP.
5. Used as a fuel in the **C**ardiac muscle. (oxidized ⇨ **energy**).

O_2 debt:

- It is **extra**-amount of O_2 needed in the period of **recovery** (**above** the normal O_2 consumption during the same period of rest).
- It is used for **oxidation of the accumulated lactic acid**.

🕮 Phases of pH changes during contraction:

1) **Acidic:** due to hydrolysis of ATP ⇨ H_3 PO4. **First**
2) **Alkaline:** due to creatine phosphate ⇨ creatine. **Then**
3) **Acidic:** due to glucose ⇨ lactic acid. **Finally**

[IV] THERMAL CHANGES

1) **Resting heat:**
   - It is the heat produced by the muscle at rest due to muscle tone.
2) **Initial heat:**
   - During muscle activity:
     a) **Activation heat:** due to chemical processes that produce & maintain contraction.
     b) **Shortening heat:** due to muscle shortening (isotonic contraction).
     c) **Relaxation heat:** extra-heat produced due to relaxation.
3) **Recovery heat:**
   - Due to chemical processes that restore chemical composition of muscle.
   - It is equal to initial heat & continue for 30 minutes.

RIGORS (CONTRACTURE)

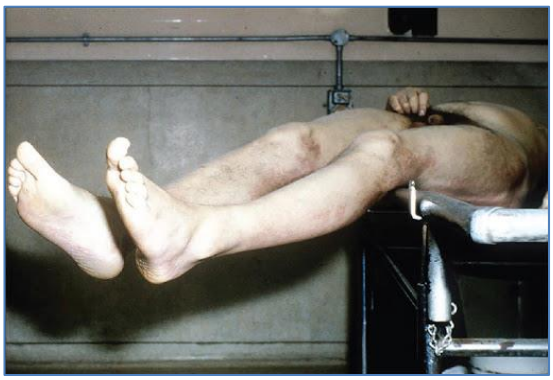
📖 Definition:

- It is a **S**tate of **S**tiffness (**S**ustained contraction) in the muscle but **why** ? ☺
  due to failure of relaxation ☹

📖 Types:

1) Rigor mortis:

- It is a state of stiffness in the muscle **after death**.
- Starts **5 hours** after death due to depletion of ATP which is required for muscle relaxation.
- **Disappears within 15-25 hours due to** autolysis of the muscle proteins by lysosomes and bacterial putrefaction.
- It is important **Medico legally** to determine the time of death.



2) Ca^{++} rigor:

- ⇧ Extracellular **Ca**$^{++}$ may stop the **heart** in the **systole**.
- Occurs in **C**ardiac muscle as it depends on **ECF** Ca^{++}.
- So, Ca^{++} injection must be very slowly.
- **Baby ? take care** ☺ → Not occur in skeletal muscle as it depends on ICF Ca^{++}.

3) Heat rigor:

- In case of increase body temperature as ⇨
- destruction of enzymes responsible for relaxation.
- coagulation of muscle protein.

4) Physiological rigor: (Contracture):

- Means contraction **not** preceded by stimulation and **not** followed by **spontaneous** relaxation.
- Occurs in extreme fatigue or untrained muscle.
- ⇩ ATP ⇨ sustained contraction.

Contraction	Contracture
Shortening of muscle.	**Shortening of muscle.**
Preceded by proper stimulation.	**Not preceded by stimulation.**
Followed by relaxation.	**Not followed by spontaneous relaxation.**

[V] MECHANICAL CHANGES

Preload

is the load on a muscle in a relaxed state, i.e., before it contracts.

Applying preload to muscle does 2 things:

• **Stretches** the muscle and stretches the sarcomere. So → The **greater** the preload, the **greater** the stretch of the sarcomere.

• **Generates passive tension** in the muscle: Muscle is elastic and "resists" the stretch applied to it.

The force of this resistance is measured as passive tension. The **greater** the preload, the **greater** the passive tension in the muscle.

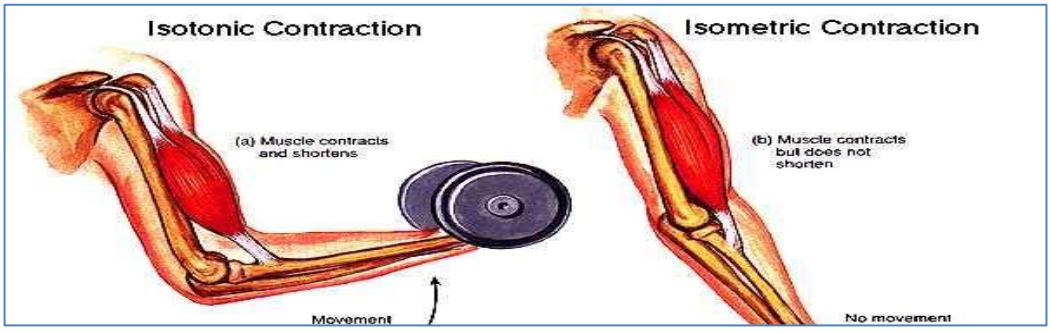
Afterload

is the load the muscle works against.

If one wants to lift a 10 Kg weight, then this weight represents the afterload. Using the 10 kg weight example, 2 possibilities exist:

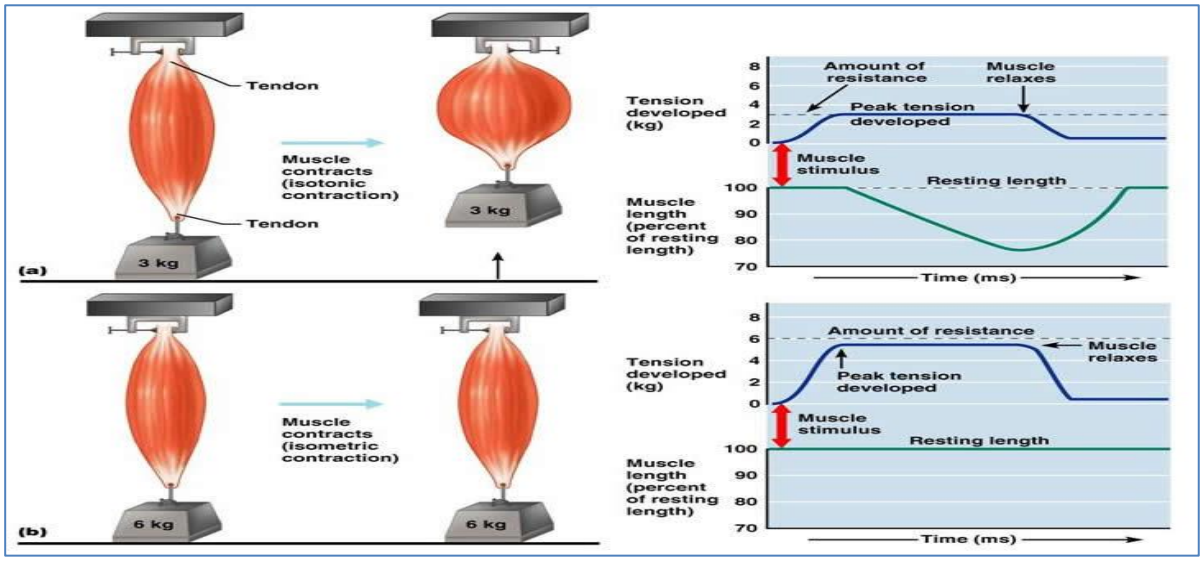
• If the muscle generates **more** than 10 kg of force, then the weight moves as the muscle shortens. **This is an isotonic contraction**

• If the muscle is **unable** to generate more than 10 kg of force, then the muscle won't shorten. **Still in isometric contraction.**



🕮 Types of contraction:

	Isometric contraction	Isotonic contraction
Muscle length	**Constant**.	Decrease.
Muscle tension	Increased.	**Constant**.
Work	**No** work is done.	Useful work is done.
Energy Consumption	**L**ess energy. **L**ost as waste heat.	Greater energy. Used for work & waste heat.
O_2 required	**L**ess.	Greater.
Sliding	**L**ess.	Greater sliding.
Duration	**L**ess duration (Short).	Longer duration (Long)
M.E.	**Zero** (no work done).	25-30% .
Heat production	**Greater**. (waste heat).	Less.
e.g.	When weight is too heavy to be moved.	Contraction of biceps to lift objects.



- When the muscle is stimulated to elevate a load, the two types occur:
  - **At first: Isometric** contraction to produce tension equal to the load.
  - **Then: Isotonic** contraction to elevate the load.
- **In isometric contraction:** (CE) shortens but (SE) stretched and elongated.
  So, the total muscle length is constant.
- **In isotonic contraction:** (CE) shortens but (SE) not stretched.
  So, the total muscle length is shorten.

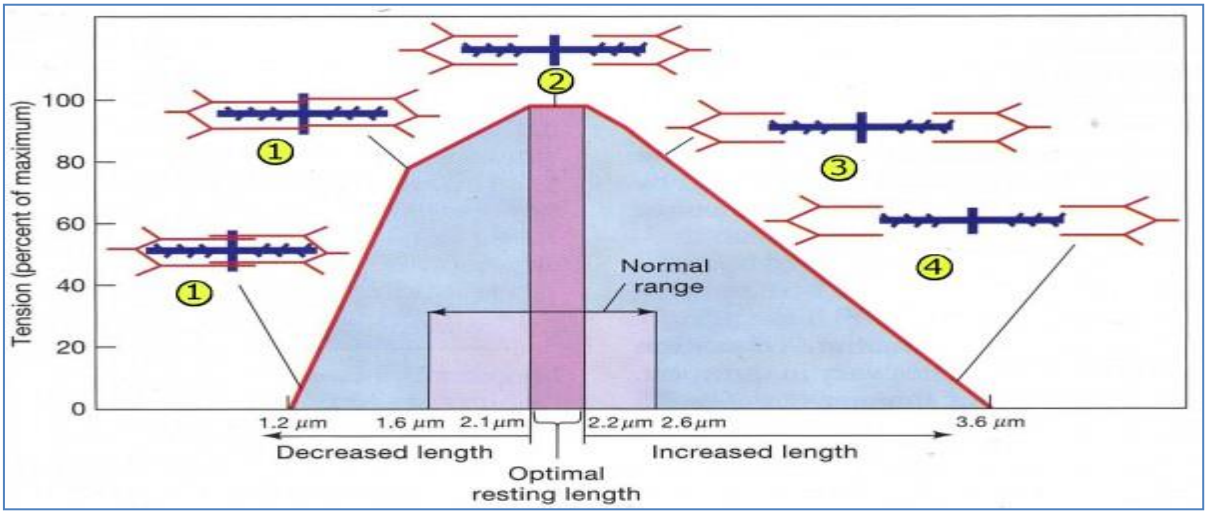
عندما تتخذ القرار الصحيح لا تبالي لقلبك ؛ تألم يوم ، شهر ، بقرار عقلي صحيح أفضل من أن تتألم طيلة حياتك بقرار خاطئ من قلبك.

🕮 Mechanical efficiency (ME):

- **Definition:** Useful work done / total energy expenditure.
- **Value:** 25 – 30% (the rest lost as heat).
- **Factors affecting:**
  1. Type of food (⇧ in CHO).
  2. Type of contraction (⇧ in isotonic contraction).
  3. Training ⇨ ⇧ ME.
  4. Temperature ⇨ ⇧ ME.
  5. Velocity of contraction (the best at 30% of maximal velocity).
- **⇧ ME means** utilization but **⇩ ME means** consumption.
- **⇩ ME in the heart** means heart failure.

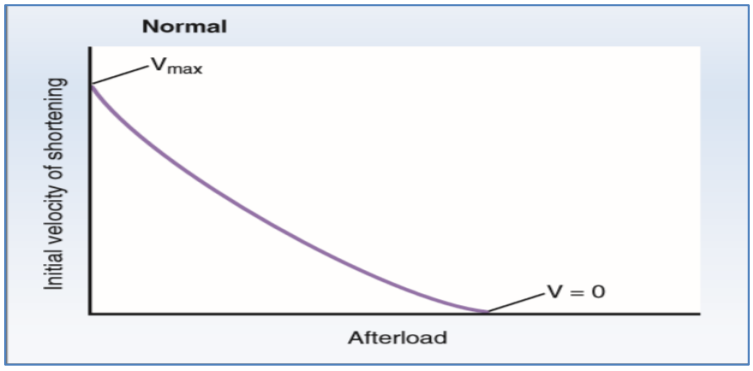
🕮 Relation between muscle length and tension (Starling law):

- Strength of muscle contraction (in isotonic contraction) and the **developed tension** (in isometric contraction) are **directly proportional** to **initial length** of muscle (**preload**) up to **limit**.
- ⇧ Muscle length ⇨ ⇧ number of cross bridges ⇨ ⇧ tension.
- But, **overstretching** ⇨ **⇩ number of cross bridges** ⇨ ⇩ tension.
- This law is myogenic law (depend on the muscle not on the nerve supply).
- This law is applied also in the cardiac and smooth muscles.



🕮 Relation between the load and velocity of contraction:

- The **velocity** of contraction is **inversely** proportional to the load carried.
- This depends on the **afterload**.
  - **Maximal velocity** is obtained when the afterload is **zero**.
  - **Zero velocity** when the afterload is **more than** power of contraction.



🕮 Muscle length:

1) **Resting length:** is the length of unstimulated muscle.
2) **Equilibrium length:** is the length of relaxed and detached muscle from bony attachment.
3) **Optimal length:** is the length at which we get the best contraction.

🕮 Muscle tension:

1) **Passive (rest) tension:** is that exerted by unstimulated muscle.
   developed by simply stretching a muscle by load to different lengths
2) **Active tension:** is the increase in tension during contraction.
   It represents the active force depending on cross-bridge cycling.
3) **Total tension:** = passive t. + active t. in isometric contraction.

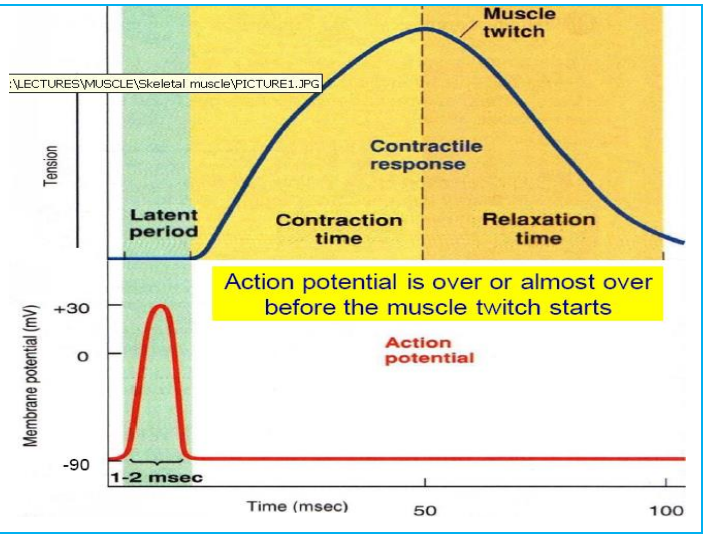
The Simple Muscle Twitch

🕮 Definition:

- It is the response of the muscle to a Single Maximal sTimulus.

🕮 Phases:

1. **Latent period**: About (**0.01 sec**).
- It is time between application of stimulus & appearance of response.
- **Due to:**
  - Conduction of impulse in nerve & Production of MEP potential
  - Conduction of impulse in the muscle & Contraction.
  - Time of recording.
2. **Contraction** phase: About (**0.04 sec**).
3. **Relaxation** phase: About (**0.05 sec**).



🕮 method:

- Nerve muscle preparation (sciatic – gastrocnemius frog muscle).

Factors affecting the simple muscle twitch: (SMT)

1. Type of muscle fiber:

- There are 2 types of muscle fibers:

Red fibers (Type I)	White (pale) fibers (Type II)
Rich in **M**yoglobin (red).	Poor in myoglobin (pale).
More blood supply.	Less blood supply.
Contain large number of **M**itochondria.	Contains few number of mitochondria.
Fibers are **S**mall in size & **S**low.	Fibers are large in size & fast.
Supplied by **S**mall, **S**low nerve.	Supplied by large rapid nerve.
Respond **S**lowly. But with long duration.	Respond rapidly. But with short duration.
Depend on **Aerobic** metabolism.	Depend on Anaerobic metabolism.
Not early fatigued.	Early fatigued.
Adapted for **Prolonged** activity. (**Static** function).	Adapted for rapid, fine activity. (**Phasic** function).
e.g. Antigravity muscles to maintain body posture.	e.g. Extra-ocular muscle. & Muscles of the hand.
Most muscles contain both types but one is predominant	

2. Temperature:

- Warming of the muscle as in muscular exercise leads to stronger and rapid contraction due to:
  a) Acceleration of the chemical reactions.
  b) Decrease the muscle viscosity.
- But overheating (>45°C) ⇨ heat rigor (stiffness).

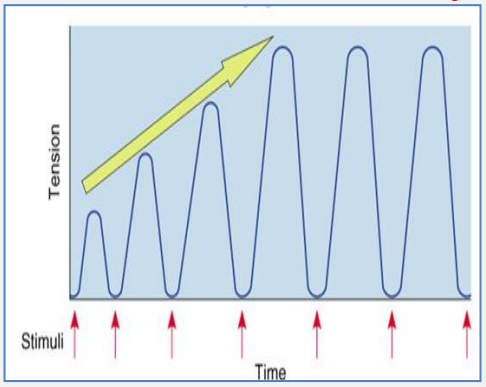
3. Initial length:

- **S**tarling law (see before).

4. Stair-case (treppe) phenomenon:

- It is **gradual** increase in muscle contraction until plateau.
- This occurs by **repeated** stimulation (application of series of maximal stimuli **just after relaxation period** of each muscle twitch).
- It occur in the skeletal and cardiac muscle.
- **This is due to:**

a) ⇧ Ca^{++} intracellular.
b) ⇧ Temperature of the muscle.
c) ⇧ Na^{+} & ⇩ K^{+} intracellular
⇨ ⇧ Ca^{++} release from sarcoplasmic reticulum.



5. Muscle fatigue:

- **Definition:**
  It is the gradual **decrease in the strength** of muscle contraction and **prolonged** duration of all phases of the SMT, especially relaxation.
- **Due to:** repeated and strong stimulation of the muscle.
- **The effect of fatigue:**
  1. Decrease strength of muscle contraction and prolonged duration of contraction and incomplete or absent relaxation.
  2. Contracture may occur with fatigue due to ⇩ ATP.
- **The causes of fatigue:**

➢ **In living muscle (after exercise)**, fatigue is due to:
a) ⇩ Blood supply to the muscle.
b) ⇩ Energy sources ATP
c) ⇧ Metabolites as CO_2 & lactic acid.

وَآخَرُونَ اعْتَرَفُوا بِذُنُوبِهِمْ خَلَطُوا عَمَلًا صَالِحًا وَآخَرَ سَيِّئًا عَسَى اللَّهُ أَن يَتُوبَ عَلَيْهِمْ ۚ إِنَّ اللَّهَ غَفُورٌ رَّحِيمٌ. صدق الله العظيم ..

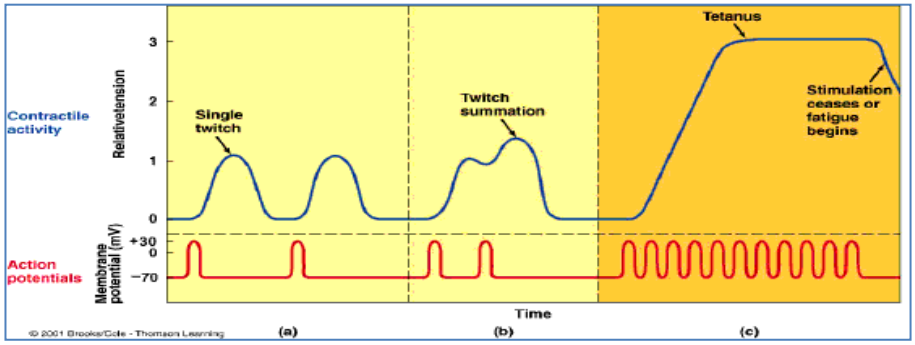
Summation of muscle contractions

- the muscle respond to another stimulus during either contraction or relaxation ⇨ summation of contraction.
- **Why ? baby .. remember** → the contraction phase in the skeletal muscle starts **after** the **A**bsolute **R**efractory **P**eriod,

📖 Effect of two successive stimuli:

- If the 2nd stimulus falls in relation to preceding one:

1) During the latent period	⇨	No response (during ARP).
2) During the contraction period	⇨	More strong contraction.
3) During the relaxation period	⇨	2 Peaks contraction.
4) Just after the relaxation period	⇨	Stair-case phenomenon.
5) After relaxation period	⇨	Normal second contraction.



🕮 Effect of multiple successive stimuli:

- According to the **frequency** of stimulation.

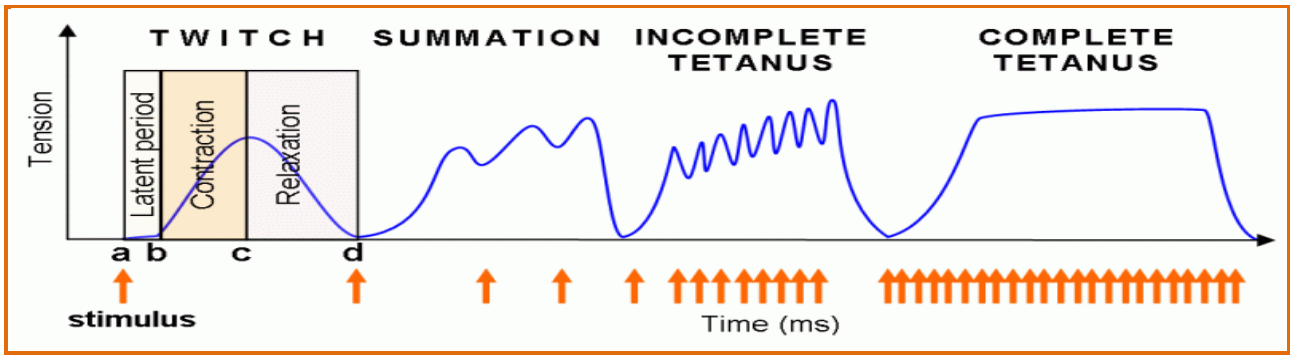
1) If the frequency is low ⇨ separate twitches with (**stair - case phenomenon**).

2) If the frequency increases and stimuli falls during **relaxation** phase of preceding twitch ⇨ **clonus** (**incomplete tetanus**).

3) If the frequency increases and stimuli falls during **contraction** phase of preceding twitch ⇨ **complete tetanus** (**sustained contraction**).

- ***" cardiac muscle → cannot be tetanized "***
- ***Skeletal muscle → contraction is tetanic***
- ***Smooth muscle → contraction is tonic***

- **Cooling & fatigue & anticholinesterase change clonus into tetanus**.
- **Warming & rest cause the reverse**.



factor influencing force of contraction :

1- activation of large number of muscle fibers
2- large sized muscle fibers
3- high frequency of stimulation
4- stretch sarcomere to optimal length

ELECTROMYOGRAPHY (E.M.G)

🕮 Definition:

- It is the recording of the electrical activity of skeletal muscle.

🕮 Method of recording:

- By 2 electrodes:
  1. One on the skin covering the muscle.
  2. The other under the skin or inside the muscle (needle electrodes).

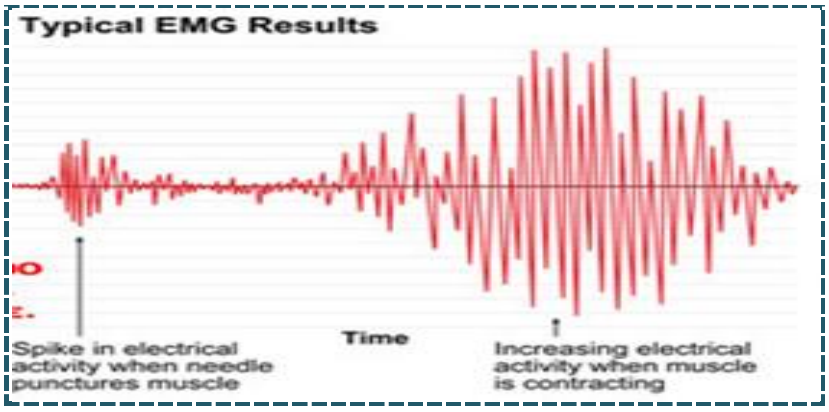
🕮 Normal electromyogram:

A. During rest:

- Small potential like (**base line**) due to mild contraction of muscle.

B. During muscular activity:

1. With minimal activity: a few motor units discharge and by increasing the effort, more units are brought into action.
2. In mild & moderate activity: the wave of potential changes can be identified.
3. In severe muscular activity with tetanic contraction: the waves are not identified (**interference pattern**).


Typical EMG Results
Time
Spike in electrical activity when needle punctures muscle
Increasing electrical activity when muscle is contracting

🕮 Abnormal EMG:

A. During rest:

- Appearance of abnormal waves during rest as **biphasic** action potential or **+ve sharp wave** (due to fibrillation).

B. During muscular activity:

- **Absence of** interference pattern during maximum contraction indicate muscle weakness as in cases of peripheral neuritis.

🕮 EMG is used for diagnosis of diseases:

1. In diseases of AHCs and nerve, there is (⇧ duration & ⇩ amplitude).
2. In diseases of muscle, there is (⇩ duration & ⇧ amplitude).

REMODELING OF THE MUSCLE TO MATCH FUNCTION

1. Muscle training (hypertrophy):

- It is the increase in size of the muscle due to:
  ⇧ Muscle **fibers thickness** & ⇧ **number of myofibrils** & ⇧ energy sources.
- Prolonged over activity ⇨ ⇧ **M**yoglobin & ⇧ **M**itochondria & ⇧ capillaries in muscle with **M**ore blood supply.

2. Muscle length:

- If the muscle is stretched this lead to **increase in number of sarcomeres**.
- The opposite occur by shorting of the muscle.

3. Muscle atrophy:

- The muscle decrease in size due to:
  a) Lesion of its motor nerve
  b) Disuse atrophy as fractured limb.
  Why ? due to decrease protein synthesis ..
  but it's **not** permanent , can be reversed by resistance training " الجيم يعني

4. Reaction of muscle to denervation:

- Injury of the motor nerve of a skeletal muscle leads to:

1) Flaccid paralysis:

- Loss of movements and decrease tone of the muscle.

2) Atrophy of the muscle:

- The muscle decrease in size within 2-4 months and the muscle fibers replaced by fibrous tissue with decrease in blood supply & myoglobin & mitochondria.

3) Muscle Fibrillations:

- Fine irregular contractions of muscle **fibers**.
- **Invisible** by the naked eye but recorded by EMG.
- They are due to **denervation hypersensitivity**.
- They are a sign of muscle degeneration.
- If the motor nerve regenerates, fibrillation disappears.

4) Muscle Fasciculation:

- Fine **visible** jerky irregular contractions of muscle **fascicles**.
- As fibrillation but visible (in fascicles).

اللَّهُمَّ إِنِّي أَعُوذُ بِكَ مِنْ زَوَالِ نِعْمَتِكَ، وَتَحَوُّلِ عَافِيَتِكَ، وَفُجَاءَةِ نِقْمَتِكَ، وَجَمِيعِ سَخَطِكَ

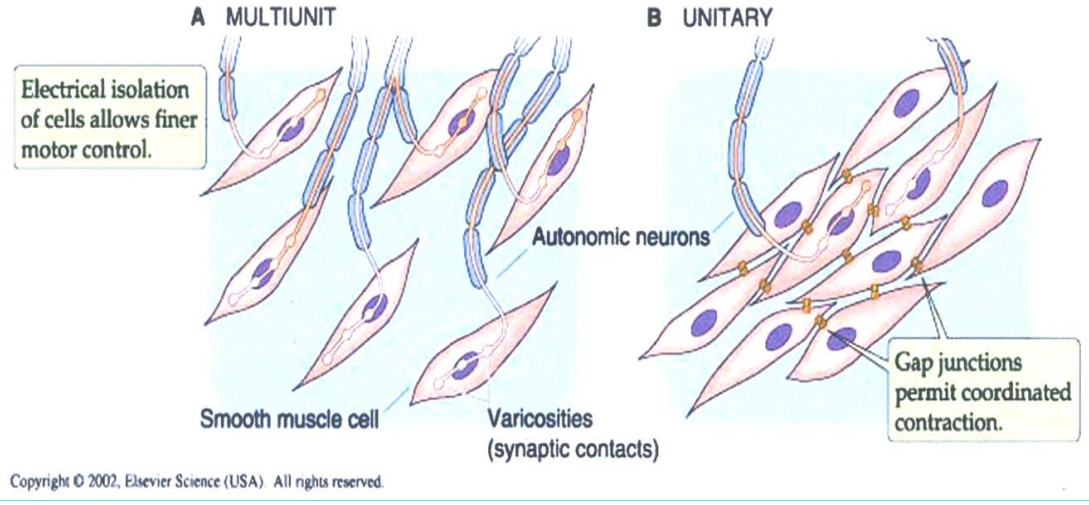
SMOOTH MUSCLE

🕮 Structure of S.M:

- SM has **more actin** filaments
- SM contain **less** mitochondria and endoplasmic reticulum.
- SM contain **calmodulin** instead of troponin-tropomyosin.
- SM innervated by **autonomic** nervous system.

🕮 Types of S.M:

Multi unit S.M.	Single unit S.M. (Unitary)
Separate fibers **without connection**.	Fibers attached by **gap junctions**. (Functional **Syncytium**).
One nerve for **each** fiber.	One nerve for **many** fibers.
Not obey all or none law.	Obey **all or none** law.
Rare spontaneous contraction. But controlled by nerve impulses.	Contract **Spontaneously**.
Not respond to stretch.	Respond to **Stretch**.
Sensitive to chemical transmitter.	**Less** sensitive.
e.g. iris in the eye, wall of blood vessels.	e.g. wall of viscera.


A MULTIUNIT
B UNITARY
Electrical isolation of cells allows finer motor control.
Autonomic neurons
Gap junctions permit coordinated contraction.
Smooth muscle cell
Varicosities (synaptic contacts)
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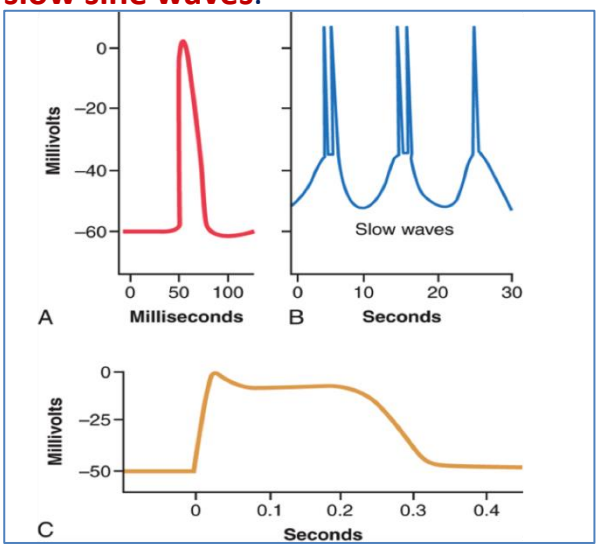
🕮 Innervations of S.M:

- No motor end plate.
- At nerve endings (sympathetic or parasympathetic) there are special nodes via it neuromuscular transmission occurs according to transmitter & receptors.
  - ➢ Depolarization ⇨ excitation ⇨ contraction.
  - ➢ Hyperpolarization ⇨ inhibition ⇨ relaxation.

🕮 Excitability of S.M:

A. RMP:

- Is **unstable** and about -40 to -60 mV. With **slow sine waves**.



B. Action potential of four types:

1) Spike potential:

- Present in the **Single unit** fibers
- (similar to AP in skeletal muscle).

2) Spike potential with Serrations:

- Present in **small intestine**.

3) Action potential with Prolonged Plateau:

- Present in **uterus**.
- (similar to AP in cardiac muscle).
- Due to delayed prolonged repolarization.

4) Pacemaker potential: (Pre potential or slow - wave potential):

- Due to **rhythmic activity of Na^+ - K^+ pump**.
- When the wave reach the firing level (-35 mv)
  ⇨ action potentials which spread over the muscle.
- (similar to the automatic cardiac fibers).

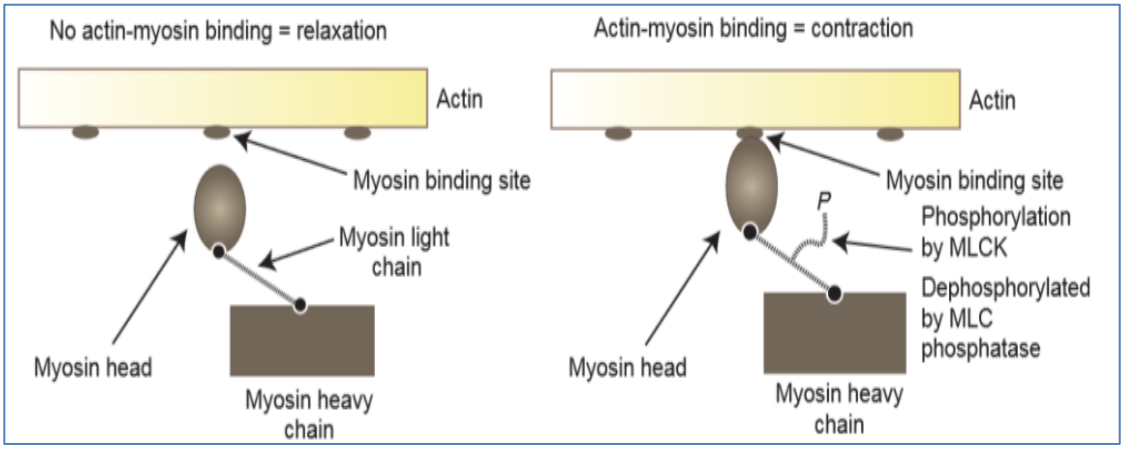
C. Ionic base of action potential:

- Depolarization may be due to **Na^+ influx** or **Ca^{++} influx** or **both**.

🕮 Excitation contraction coupling of S.M:

A. Contraction:

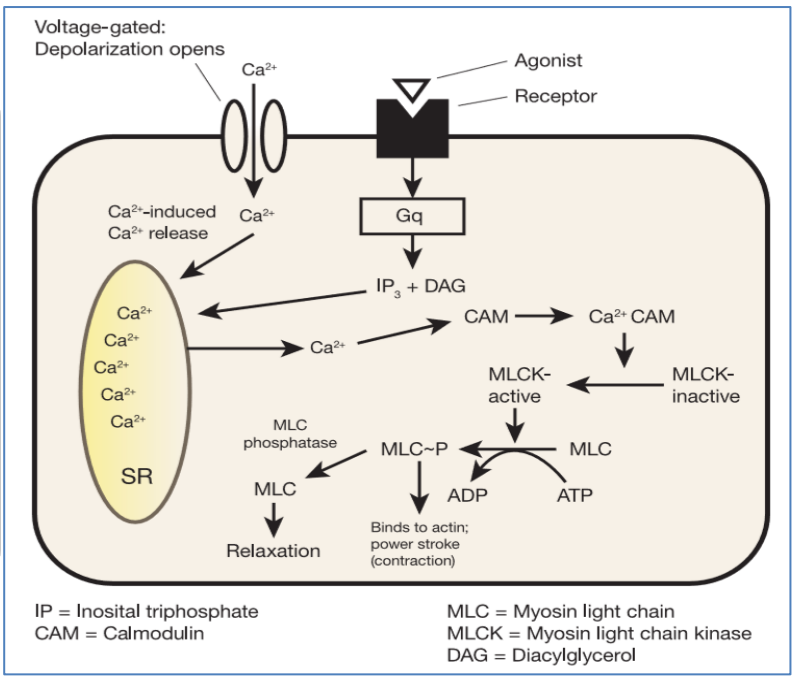
Extracellular Ca^{++} influx or intracellular Ca^{++} release from endoplasmic reticulum ⇨ ⇧ Ca^{++} ⇨ combine with **calmodulin** ⇨ activation of **Myosin light chain kinase** enzyme (**MLCK**) ⇨ **phosphorylation of the light chain of myosin** → makes **myosin** in a high-affinity state for actin ⇨ binding of actin & myosin ⇨ **shortening (contraction).**



B. Relaxation:

⇩ Intracelular Ca++ (**by Ca++ pump**) ⇨ stimulation of **Myosin light chain phosphatase** → dephosphorylates myosin → **reducing** the affinity of myosin for actin → **causing relaxation**

☺ **NOTE ***
cAMP , cGMP inhibit MLCK



🕮 Characters of S.M contractility:

1. **S**pontaneous contraction but under nervous regulation.
2. **S**low Energy and O_2 consumption and depends mainly on **anaerobic** glycolysis.
3. **S**low Excitation - contraction coupling ⇨ **S**luggish contraction.
4. **S**low Ca^{++} pump ⇨ contraction is maintained longer than in skeletal muscle.
5. **S**low cycling of cross bridges.
6. **S**low onset of contraction and relaxation.
7. SM has great ability to **S**horten as far greater percentage of its length.
8. **LATCH** mechanism, as prolonged tonic contraction needs less energy, less nervous or chemical stimulation than initial activity.
   So, this delays fatigue.
9. **S**tress relaxation (**plasticity**): in which if SM is slowly stretched ⇨ increased tension at first then the tension gradually decreases in spite of continuous stretch (e.g. the urinary bladder can receive large volumes of urine without marked increase in wall tension).
10. Visceral SM **S**hows:
    a) **Tone:** continuous mild contraction.
    b) **Rhythm:** due to repetitive discharge of spike potentials.

📖 Factors affecting excitability & contractility of S.M:

	⇧ Excitability ⇨ Contraction	⇩ Excitability ⇨ Relaxation
ANS	Parasympathetic.	Sympathetic.
Drugs	Parasympathomimetics. Sympatholytics.	Parasympatholytics. Sympathomimetics.
Temperature	**Cooling**.	**Warming**.
pH	Alkalosis.	Acidosis.
Ions	⇩ Ca^{++} & ⇧ K^{+}.	⇧ Ca^{++} & ⇩ K^{+}.
Stretch	Rapid moderate stretch.	Severe stretch.
Osmotic pressure	Low.	High.
Hormones	Vasopressin & Oxytocin & Estrogen.	Catecholamines & Progesterone.

	Smooth Muscle	Skeletal muscle
striation	**Non** striated	Striated " Sarcomeres "
Contractile	**More** Actin	Present
Regulatory protein	**Calmodulin**	Troponin - tropomyosin
SarcoTubular system	**No** T-tubules	Contain T-Tubules
Nerve :	**Autonomic** nervous system	Voluntary control " Somatic nerve
RP	**Un**-stable " from -40 to -60 "	Stable " -90 "
Ionic Basis	Ca from Extra-cellular **or** Endoplasmic reticulum	Ca mainly from Sarcoplasmic reticulum
Glycolysis	Mainly **Anaerobic**	Aerobic – Anaerobic
Others :	**Slow** Ca pump **Slow** contraction – relaxation **Delayed** fatigue " Latch "	Rapid Ca pump Rapid Contraction – relaxtion May be fatigued

NEURO-MUSCULAR TRANSMISSION

🕮 Definition:

- The area of **contact** between a **somatic nerve fiber** and **muscle fiber** is called neuromuscular junction or Motor End Plate (MEP).

🕮 Structure of the motor end plate (MEP):

1. Presynaptic membrane of motor nerve:

- The nerve loses myelin and branches to many ***sole foots*** (to increase surface area).
- Contain large number of **Ach vesicles**, mitochondria .

2. Synaptic cleft:

- It is a distance (**200-300 A°**) between the two membranes.
- Contain **cholinesterase** enzyme which hydrolyze the Ach.

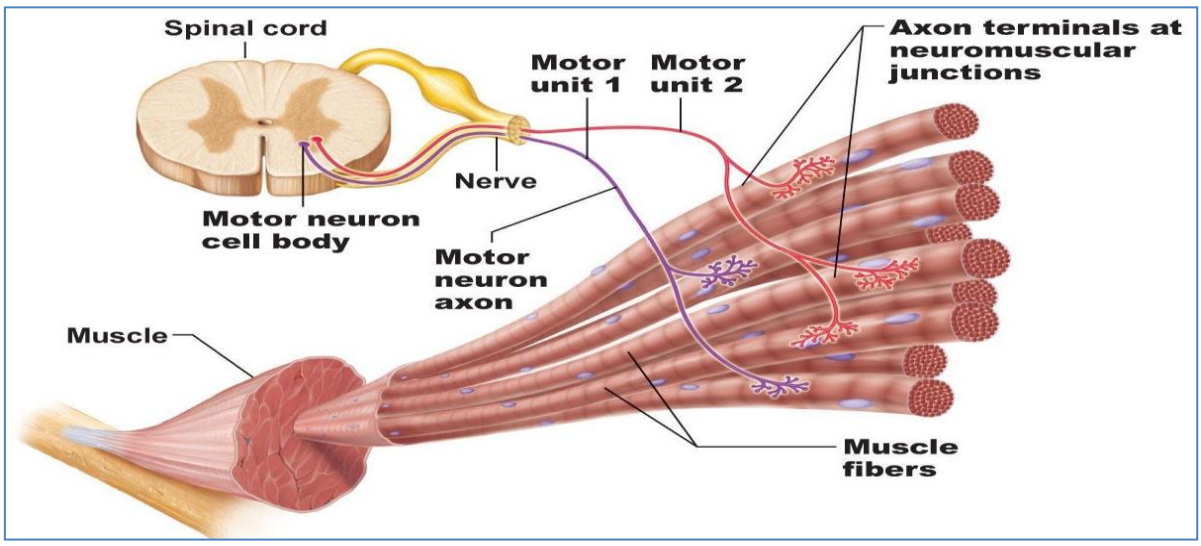
3. Postsynaptic membrane of muscle fiber:

- Membrane has invaginations called ***synaptic gutter*** (to increase the surface area).
- Contain **Ach receptors**. (**nicotinic Nm receptors**).

🕮 Neuromuscular innervations:

Motor unit: consists of **one** AHC + its axon + muscle fibers supplied by this axon. (**obeys all or none law**). (one nerve fiber / 3-300 muscle fibers).

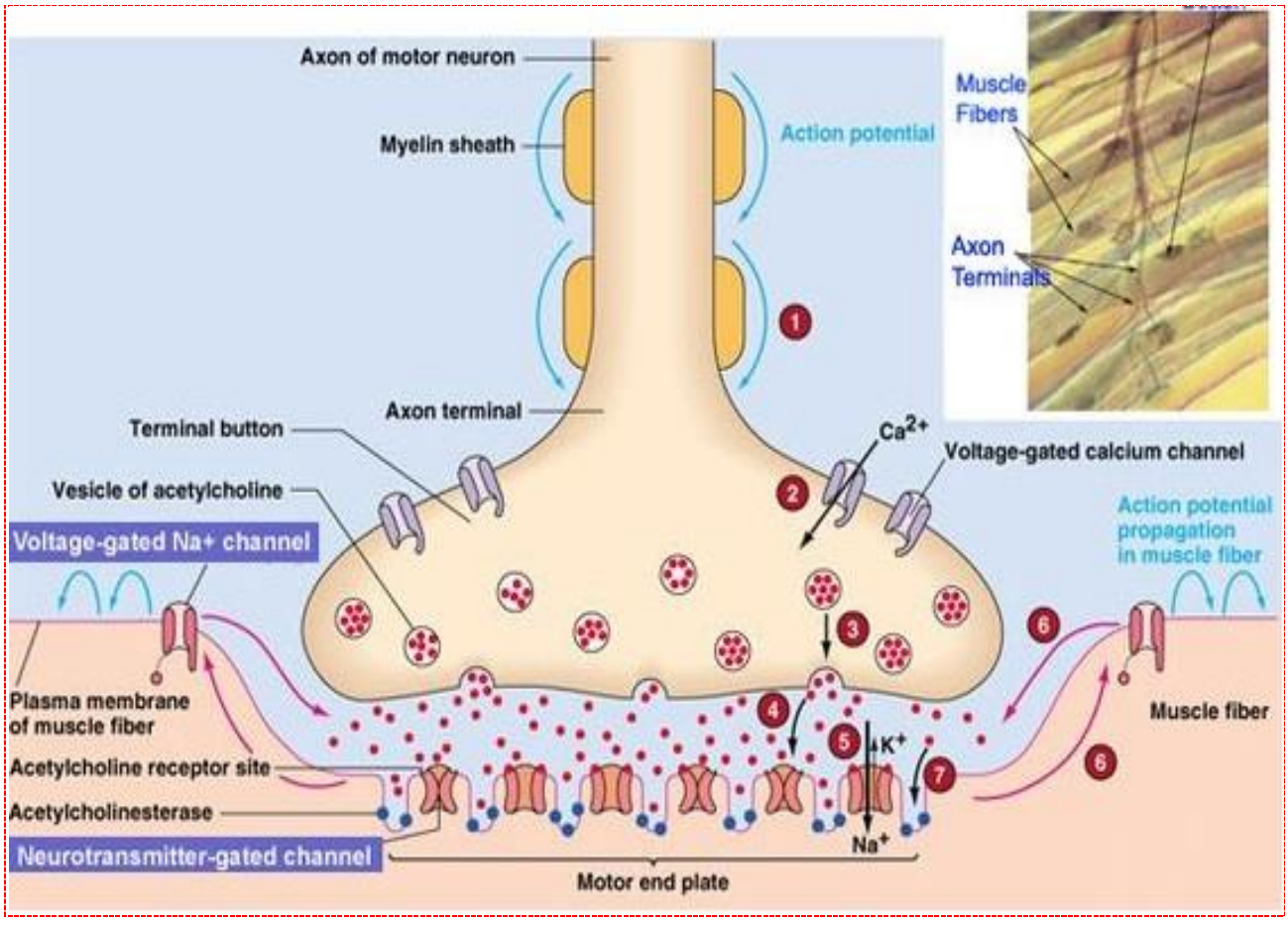
Motor pool: consists of **all** AHCs + their axons + skeletal muscle supplied by them. (**not obey all or none law**).



🕮 Neuromuscular transmission (The end plate potential):

6. Stimulation of the nerve causes **Ca^{++} influx** into nerve terminals via **voltage gated Ca^{++} channels**.
7. fusion of Ach vesicles to the "release site" at the presynaptic membrane ⇨ rupture of Ach vesicles and release of Ach by **exocytosis**.
8. Ach passes into the synaptic **cleft**.
9. Ach combines with **specific receptors** in the muscle membrane.
10. This increases **Na^{+} influx** into the muscle via **chemical gated Na^{+} channels** ⇨ partial depolarization of MEP called **End Plate Potential (EPP)** when reaches the **firing level** an **action potential** is produced.
11. The AP **spread** along the muscle fiber in both direction.
12. Then, repolarization occurs by: ⇧ K^{+} outflux & Na^{+} - K^{+} pump.
13. Finally, Ach is rapidly hydrolyzed by **cholinesterase** enzyme in the cleft to prevent re-excitation of the muscle.

Miniature end plate potential (MEP): Spontaneous rupture of Some Ach vesicles ⇨ Subthreshold depolarization in MEP without action potential in the muscle fiber (not reaching the firing level).



🕮 Properties of neuromuscular transmission:

1) UniDirectional:

- The impulse passes in **one direction** only from the nerve to the muscle.
- Because the nerve contains the Ach & the muscle contains the receptors.

2) Synaptic Delay:

- It is the time needed for the release of Ach and its effect on the muscle.
- Synaptic delay = **0.5 msec**.

3) Fatigue:

- May occur due to repeated stimulation ⇨ **exhaustion of Ach** (⇩ of Ach).

4) The 10 Folds safety Factor:

- Number of Ach molecules released is **10 times** more than number of receptors.
- To make sure that any nerve impulse will produce muscle depolarization.

5) Effect of drugs (see ANS):

See pharmacology

6) Effect of ions:

- ⇧ Ca^{++} influx into nerve ⇨ ⇧ release of Ach ⇨ ⇧ transmission.

MYASTHENIA GRAVIS

Definition:

- **Hereditary** disease which affects **females** more than males.
- Characterized by marked weakness and easy fatigability of muscles.
- If affect respiratory muscles ⇨ death.

Causes: 1) ⇩ Ach synthesis. 2) ⇩ Ach release at MEP.
3) ⇩ Ach receptors. 4) ⇧ Activity of cholinesterase enzyme.
5) Presence of curare – like substance in the blood.
6) Autoimmune disease (presence of antibody against Ach ion channels).

Treatment:

1) Rest.
2) Anti cholinesterase drugs e.g. **PROSTIGMINE**.
3) If autoimmune, surgical removal of thymus gland is required.
4) Cortisone may be used.

Other types of myasthenia: a)Secondary myasthenia: due to bronchogenic carcinoma.
b) Neonatal: in some babies but for short time (2-6 weeks).

Myopathies:

It is progressive degeneration of **muscle** due to endocrinal, metabolic or toxic causes.